Graft-Versus-Host Disease

What Is Graft-Versus-Host Disease?

Patients who receive a stem cell transplant from an identical twin donor, are infused with stem cells that are truly identical to their own. All other recipients of donor stem cells, whether from HL:A-identical sibling donors, or from matched unrelated donors, will be infused with stem cells that are different from the patient's own stem cells. The human immune system is based on recognition of "self" against "different or "foreign". Immune systems are trained to attack and destroy "foreign" proteins, whether they are bacteria, viruses, cancer cells, or transplanted tissues. Thus, the differences between the tissues of the patient and the stem cells of the donor lead to a fight and attempts of one to destroy the other. The patient's tissues (host tissues) will try to destroy the stem cells. This process is called "rejection" and is more frequent as the donor and recipient are less well matched. Rejection of the stem cells results in failure of the new stem cells to grow and produce sufficient blood cells. The patient continues to have low white cell and platelet counts and continues to be at risk of infection and bleeding. Repeating the transplant is the only way of helping the patient. Often the re-transplant does not succeed in raising the white cells fast enough to prevent fatal infections. Fortunately, rejection is uncommon, since the issues of the patient have been suppressed by the chemotherapy and radiation given to destroy the malignant cells ("preparative regimen").

A "reversed rejection" can also occur. Under this scenario, the healthy donor stem cells recognize the patient's tissues as foreign and attack them. This is the "transplant against the patient", or "Graft-versus-Host" reaction. The complications is called "Graft-versus-Host Disease" (GvHD).

What *Types* Of GvHD Exist?

Commonly, GvHD is divided into *acute* GvHD and *chronic* GvHD. Acute GvHD occurs within the first 100 days after transplant, but most often between 15 and 40 days after stem cell infusion. Chronic GvHD occurs beyond day 100 after transplant. Acute GvHD can lead to chronic GvHD, but chronic GvHD may occur without any evidence of previous acute GvHD. The chronic variant of GvHD may occur up to several years after transplant, indicating that the "fight" between donor stem cells and patient tissues can continue for years. In fact, at some level the fight between donor and recipient will never stop. The donor stem cells will never feel completely at home. In patients receiving a graft from an HLA-identical sibling, ultimately the donor stem cells will function quite normally. Patients who received grafts from HLA- mismatched donors will remain at an increased risk of infections for many years.

What Are The *Symptoms* Of Acute GvHD?

When acute GvHD develops, white cells ("lymphocytes") from the stem-cell graft move towards target tissues. Through direct contact or through proteins produced by these cells ("lymphokines"), the target tissues get damaged. The major targets are the skin, bowel, and liver. The skin is often the first tissue that shows signs of attack. Skin rash develops, often starting on the palms, soles, and behind the ears. Other parts of the body, such as scalp, upper chest and back, and abdomen may follow. Some patients will have redness of their entire skin. A skin biopsy (small biopsy of skin, about 1/8" in diameter) usually confirms the diagnosis, but the clinical picture is quite typical.

The second tissue that can be involved is the bowel. This leads to diarrhea and abdominal cramps. The diarrhea is caused by loss of cells that cover the inside of the bowel, leading to loss of fluids and proteins from the body. The small bowel, particularly the last part of it (jejunum and ileum), is the main target of the GvHD reaction. Cramps start when a large area of bowel has lost its cover ("mucous membrane") and peristalsis becomes less organized. Diarrhea can vary from one loose stool a day to 2 gallons of diarrhea! In severe cases of diarrhea, it is difficult to support the patient through the loss of fluid and nutrients. The damaged gut is also an easy entry port for bacteria and

fungi.

The third tissue involved by acute GvHD is the liver. Patients develop jaundice, because the bile ducts become clogged and bile backs up into the blood instead of being excreted into the bowel. The jaundice is itself not life-threatening, but the liver can be damaged by the GvHD reaction. Other tissues, such as lung, adrenal glands, and pancreas can also show signs of acute GvHD, but their significance is uncertain.

How Do You *Grade* GvHD?

In order to grade the severity of GvHD, a staging system was developed in the 1970's. This system, that originated at the Fred Hutchinson Cancer Center in Seattle, looks at involvement of skin, gut, and liver. The skin involvement is scored as percentage of total skin that is inflamed. Gut involvement is determined by amount of diarrhea per 24 hours, and liver involvement by the serum level of bilirubin. The mildest grade of GvHD is grade I, the worst is grade IV. Grade I has little effect on survival and may not need any treatment, whereas survival of patients with grade III or IV is clearly worse. A common cut-off is grade 0-I against grade II, III and IV.

What Is Done To *Prevent* GvHD?

Several drugs and procedures may be used to try and prevent acute GvHD. IBMT physicians use daily cyclosporine therapy to decrease the frequency and severity of acute GvHD. Cyclosporine therapy starts on the day before transplant (day –1) and is given as daily I.V. infusions over 4-14 hours. Once the patient is stable and can take oral medications, the cyclosporine is switched to therapy by mouth: the drug *Neoral®* is given twice a day. Capsules are either 100 mg or 25 mg. The switch to oral medication happens between 15 and 30 days after transplant. In most patients, Neoral is continued until at least day 90 after transplant, but in most patients this drug needs to be continued much longer.

Many patients will also receive a small number of doses of *Methotrexate* by I.V.injection (days 1, 3 ,6 and 11 after transplant), or will receive *Solumedrol®* (methyl-prednisolone) daily starting 7 days after transplant. At IBMT, patients who are at particular risk of acute GvHD, such as patients receiving stem cell grafts from unrelated or mismatched related donors, will receive grafts that have been manipulated prior to transplant. Various techniques are used to remove the T-lymphocytes from the stem cells. T-lymphocytes have been shown to be primarily responsible for acute GvHD. Currently, IBMT is using a technique in which T-cells are coated with antibodies bound to magnetic beads. The T-cells are then removed with a strong magnet.

How Do You *Treat* GvHD?

Acute GvHD of grade I does not need specific therapy, except perhaps a skin cream to decrease the inflammation. If grade II (or worse) is present, the first-line therapy are steroids. Typically, *Solumedrol®* is given through I.V. injections twice a day. When GvHD stabilizes, the *Solumedrol* is switched to oral prednsione. The dose of prednisone is slowly tapered over the next weeks to months. For acute GvHD that is unresponsive to steroids, other drugs are used. One example is *ATGAM®*, which is given by I.V. infusion daily for 4 days.

Why Is GvHD *Dangerous*?

Acute GvHD can be very dangerous, and is the single most important transplant-related cause of death after allogeneci stem cell transplant. The danger of severe acute GvHD is multifactorial. First, severe GvHD of the gut causes extensive damage to the lining cells of the bowel. Thus, micro-organisms, such as bacteria and fungi, can invade the body and may cause a fatal infection. Second, voluminous diarrhea may result in a loss of important nutrients, electrolytes, and fluid. Third, the GvHD reaction suppresses the new immune system. Finally, the treatment necessary to control the GvHD in itself will further suppress the new immune system. Therefore, many patients

suffering from severe acute GvHD will ultimately die from infections with bacteria, fungi, or viruses.

Why Is GvHD *Not "All Bad"*?

As described above, acute GvHD is a possibly dangerous complication. However, the GvHD reaction also has positive aspects. While attacking the tissues of the patient, the new stem cells will often also attack the cancer cells that still may be present after transplant. This was first documented in acute leukemia, and this phenomenon has been called "graft-versus- leukemia" effect. Similar effects have been observed in malignant lymphoma, myeloma, and perhaps even some solid tumors. For certain diseases, such as chronic myelogenous leukemia (CML), the graft-versus-leukemia (GvL) effect may well be the most important reason that allogeneic transplants are successful in curing the disease. With increasing difference between donor and patient, the risk GvHD increases. This may well mean that also the chance of GvL effect increases. In recent years, transplant physicians have learned to apply the GvL effect to treat or prevent disease recurrence *after* stem cell transplant by the infusion of donor white cells (DLI = Donoir Lymhocyte Infusions). Chronic GvHD may be even more important to prevent disease relapse than acute GvHD.

What Are Symptoms Of *Chronic* GvHD?

Chronic GvHD tends to have a much more insidious start. The skin may become hardened, and the joint less flexible. Sometimes abnormal liver function tests are the first sign, or some difficulty swallowing. Many patients develop dry mouth and/or dry eyes ("sicca syndrome"). Chronic GvHD may develop out of more acute GvHD, or may start without any history of prior acute GvHD. By definition, chronic GvHD starts after day 100, but the first symptoms may not start until 1 or 2 years after transplant.

What Are Risks Of *Chronic* GvHD?

The hardened skin and limited flexibility of joints are difficult to treat, sine they involve scarring of the skin. Therefore, preventing them with physical therapy is very important. If liver function abnormalities exist for too long, scarring of the liver may also occur. Patients with chronic GvHD continue to be at risk of serious infections. The dry mouth increases the risk of tooth decay, and the dryness of the eyes may lead to cornea damage.

What Is The *Therapy* Of Chronic GvHD?

Physical therapy, sufficient exercise, and good personal hygiene are very important in the treatment of chrnoic GvHD. Drug therapy consists of prednisone, often in combination with cyclosporine. In many patients, Imuran® (azathioprine) is also used. All these medications are given by mouth. The minimum treatment lasts 6 months, but often much longer periods of treatment are necessary.